



Complete Summary

GUIDELINE TITLE

Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of zaleplon, zolpidem and zopiclone for short-term management of insomnia. London (UK): National Institute for Clinical Excellence (NICE); 2004 Apr. 27 p. (Technology appraisal; no. 77).

GUIDELINE STATUS

This is the current release of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [March 14, 2007, Sedative-hypnotic drug products](#): Revisions to product labeling to include stronger language concerning potential risks including severe allergic reactions and complex sleep-related behaviors, such as sleep-driving.

COMPLETE SUMMARY CONTENT

**** REGULATORY ALERT ****

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES

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SCOPE

DISEASE/CONDITION(S)

Insomnia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Sleep Medicine

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the effectiveness and cost-effectiveness of zaleplon, zolpidem and zopiclone for the short-term management of insomnia

TARGET POPULATION

Adult patients with insomnia

INTERVENTIONS AND PRACTICES CONSIDERED

Hypnotic drug therapy:

1. Non-benzodiazepine hypnotics
 - Zaleplon (Sonata®)
 - Zolpidem (Stilnoct®)
 - Zopiclone (Zimovane®)
2. Benzodiazepine hypnotics

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness (e.g., sleep onset latency, total sleep duration, number of awakenings, quality of sleep, rebound insomnia)
- Cost-effectiveness
- Adverse effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group (LRIG), University of Liverpool (see the "Companion Documents" field).

Clinical Effectiveness

Search Strategy

The search included a number of strategies. The electronic databases were searched for the period from 1966 to March 2003 (See Table 3A in the assessment report). The search had no language restrictions. Search terms for electronic databases included a combination of index terms (e.g. sleep initiation and maintenance disorders or insomnia) and free text words (e.g. insomnia or sleeplessness) combined with specific drug terms (e.g. zaleplon or Sonata, zolpidem or Stilnoct, zopiclone or Zimovane). Details of the search strategies used and the number of references retrieved for each search are provided in Table A1, Appendix 1 of the assessment report.

Reference lists of retrieved articles and pharmaceutical company submissions were searched to identify further studies. Recent issues (October 2002 to June 2003) of relevant journals that might not yet have been indexed in electronic databases were handsearched; the journals searched included: European Psychiatry, Human Psychopharmacology: Clinical and Experimental, International Clinical Psychopharmacology, Psycho-pharmacology, Sleep, Sleep Medicine, Sleep Medicine Reviews, The British Journal of Psychiatry, The Journal of Clinical Psychiatry. Internet resources (including industry supported websites) were examined for information on clinical trials.

An advisory panel was established to guide the review process. The role of the advisory panel was to comment on the review protocol, to answer specific questions as the review progressed and to comment on an early draft of the review including identifying missed or ongoing studies.

Inclusion and Exclusion Criteria

The identified citations were assessed for inclusion through two stages and disagreements were resolved by discussion at each stage. Two reviewers independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved. Full text copies of the selected papers were obtained and each assessed independently by at least two reviewers for inclusion.

Details of inclusion and exclusion criteria are presented in Table 3A of the assessment report.

Extended Review on Dependence and Withdrawal Symptoms

Drug trials are usually too short to be able to assess the development of drug dependence. Therefore the research group conducted an extended search to identify studies of other designs which might help address the question of the relative potential of the comparison drugs to induce drug dependence and withdrawal.

Search Strategy, Inclusion and Exclusion Criteria

Search terms for this expanded search included a combination of index terms (e.g. withdrawal syndrome, drug tolerance, drug withdrawal) and free text words (e.g. withdrawal, dependency, tolerance, rebound) combined with specific drug names including zaleplon or Sonata, zolpidem or Stilnoct, zopiclone or Zimovane. Search strategies did not include filters that would limit results to specific publication types or study designs. Only English-language reports were identified because of time restrictions. Details of the search strategies used and the number of references retrieved for each search are provided in Table A2 in Appendix 1 of the assessment report.

Electronic databases searched and inclusion and exclusion criteria are detailed in Table 3A of the assessment report.

Methods for Reviewing Cost Effectiveness

Search Strategy

A comprehensive review of the literature was undertaken to identify all published articles that could provide evidence with regard to the cost-effectiveness of newer hypnotic drugs for the management of insomnia.

The search included a number of strategies. Search terms for electronic databases included a combination of index terms (e.g. sleep initiation and maintenance disorders or insomnia) and free text words (e.g. insomnia or sleeplessness) combined with specific drug terms (e.g. zaleplon or Sonata, zolpidem or Stilnoct, zopiclone or Zimovane). Clinical terms were combined with economic terms (e.g. cost or economic).

Reference lists of retrieved articles and pharmaceutical company submissions were also searched to identify further studies. Internet resources (including industry supported websites) were examined for information on clinical trials.

Electronic databases searched are presented in Table 3A of the assessment report. Search strategies and results of the searches undertaken are provided in Table A3, Appendix 1 of the assessment report.

Inclusion and Exclusion Criteria

The aim of the economic review was to identify economic evaluations informed by clinical data from randomised controlled trials. After scanning the abstracts, all papers that appeared to be of potential value to the study were obtained. Using explicit, predetermined criteria (see Table 3A of the assessment report), two reviewers independently identified studies for inclusion in the cost-effectiveness review process. Disagreements were resolved through discussion. The inclusion and exclusion criteria used in the review are presented below.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Clinical Effectiveness

Data Extraction

Data extraction was carried out by four reviewers. Individual study data relating to study design and findings were extracted and checked by two reviewers using a pre-tested data extraction form. Data from baseline and first night after discontinuation of treatment were extracted where more than one data point was available.

Quality Assessment

At least two reviewers independently evaluated the included studies for methodological quality. This involved methodological assessment for clinical effectiveness based on the Centre for Reviews and Dissemination, York, Report

4(81) (see Appendix 2 of the assessment report). Any discrepancies were resolved through consensus.

Extended Review on Dependence and Withdrawal Symptoms

Data Extraction

Data extraction was carried out by two reviewers. Individual study data relating to study design and findings were extracted independently by one reviewer into a pre-designed data extraction form and checked by a second reviewer.

Meta-Analysis of Results

The outcomes that were considered in the identified studies were:

- sleep onset latency
- total sleep duration
- number of awakenings
- quality of sleep
- adverse effects
- rebound insomnia (sleep onset latency, total sleep duration, number of awakenings, quality of sleep)

The studies identified were grouped and presented according to the following comparisons:

- I. Z x BZD comparisons:
 - Zolpidem versus Nitrazepam
 - Zolpidem versus Temazepam
 - Zopiclone versus Lormetazepam
 - Zopiclone versus Nitrazepam
 - Zopiclone versus Temazepam
- II. Z x Z comparisons:
 - Zaleplon versus Zolpidem
 - Zolpidem versus Zopiclone

Meta-analyses were carried out when possible between studies that compared the same drugs. If extracted data were unsuitable for combination using meta-analysis, data were shown in a forest plot. Scales used to assess outcomes differed between studies, and therefore, to avoid problems in interpretation when scale direction differed also, mean values were negated when a decreased score indicated improvement. This was carried out to create a uniform direction of improvement on the forest plots, so that an increase in mean score indicated improvement. Crossover trials with less than two nights washout were excluded from the analysis. Data were pooled using a fixed effect model (as there was no evidence of statistical heterogeneity) with odds ratio and 95% confidence intervals.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients, and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals,

patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

None of the submissions contained an economic evaluation that compared the costs and effects of the short-term use of Z-drugs with benzodiazepines. In addition, the Assessment Group was unable to identify any evaluations in the health economics literature. No comparative data on the health-related quality of life associated with Z-drugs and benzodiazepines using generic health status measures were identified, and there was no evidence to link the clinical endpoints from the trials with quality of life.

The manufacturer of zaleplon submitted two models based upon the key assumption that zaleplon does not cause 'mental impairment' the day after administration. See Section 4.2 of the original guideline document for a detailed discussion of these models.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- When, after due consideration of the use of nonpharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, it is recommended that hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications.

- It is recommended that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed.
- It is recommended that switching from one of these hypnotics to another should only occur if a patient experiences adverse effects considered to be directly related to a specific agent. These are the only circumstances in which the drugs with the higher acquisition costs are recommended.
- Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

A total of 24 randomised controlled trials (RCTs) were used to support the recommendations for clinical effectiveness.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia

POTENTIAL HARMS

Adverse effects of drug treatment including drug dependency, withdrawal syndrome, and tolerance

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- National Health Service (NHS) organisations and clinicians who prescribe treatment for people with insomnia should review their current practice and policies and the current patterns of prescribing hypnotic drugs, as reported in high-level performance indicators, to take account of the guidance.
- Local guidelines, protocols or care pathways that refer to the care of people with insomnia should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
 - Hypnotic drug therapy is used for the management of severe insomnia interfering with normal daily life only after due consideration of the use of non-pharmacological measures.
 - When hypnotic drug therapy is used, the drugs are prescribed for short periods of time only, in strict accordance with the licensed indications.
 - When hypnotic drug therapy with shorter-acting benzodiazepine hypnotics, zaleplon, zolpidem or zopiclone, is prescribed, the drug with the lowest purchase cost is chosen.
 - A patient is switched from one of these hypnotic drugs to another only if he or she experiences adverse effects considered to be directly related to a specific agent.
 - A patient who has not responded to one of these hypnotic drugs is not prescribed any of the others.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

Patient Resources

Quick Reference Guides/Physician Guides

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

Living with Illness

IOM DOMAIN

Effectiveness

Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of zaleplon, zolpidem and zopiclone for short-term management of insomnia. London (UK): National Institute for Clinical Excellence (NICE); 2004 Apr. 27 p. (Technology appraisal; no. 77).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Apr

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Dr A E Ades, Senior Scientist, MRC Health Services Research Collaboration, University of Bristol; Professor Ron Akehurst, Dean, School of Health Related Research, University of Sheffield; Dr Tom Aslan, General Practitioner, Stockwell, London; Professor David Barnett (*Chair*) Professor of Clinical Pharmacology, University of Leicester; Professor Sheila Bird, MRC Biostatistics Unit, Cambridge; Dr Karl Claxton, Health Economist, University of York; Dr Richard Cookson, Senior Lecturer, Health Economics, School of Health Policy and Practice, University of East Anglia, Norwich; Professor Gary A Ford Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust; Ms Bethan George, Interface Liaison Pharmacist, Tower Hamlets PCT and Royal London Hospital, Whitechapel; Dr Trevor Gibbs, Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford; Mr John Goulston, Director of Finance, Barts and the London NHS Trust; Professor Robert Kerwin, Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London; Professor Philip Home, Professor of Diabetes Medicine, University of Newcastle upon Tyne; Dr Terry John, General Practitioner, The Firs, London; Mr Muntzer Mughal, Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust, Chorley; James Partridge, Chief Executive, Changing Faces; Mrs Kathryn Roberts, Nurse Practitioner, Hyde, Cheshire; Professor Philip Routledge, Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff; Ms Anne Smith, Lay Representative; Trustee, Long-Term Medical Conditions Alliance; Professor Andrew Stevens (*Vice-Chair*) Professor of Public Health, University of Birmingham; Dr Cathryn Thomas, General Practitioner, and Senior Lecturer,

Department of Primary Care & General Practice, University of Birmingham; Dr Norman Vetter, Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff; Dr David Winfield, Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Zaleplon, zolpidem and zopiclone for the short-term management of insomnia. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Apr. 2 p. (Technology appraisal 77). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- The clinical and cost-effectiveness of zaleplon, zolpidem and zopiclone for the management of insomnia. Assessment report. Liverpool Reviews and Implementation Group; 2003 Aug. 139 p. Available in Portable Document Format (PDF) from the [NICE Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0545. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the [original guideline document](#).

PATIENT RESOURCES

The following is available:

- Zaleplon, zolpidem and zopiclone for insomnia. Understanding NICE guidance - information for people with insomnia, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Apr. 10 p. (Technology appraisal 77).

Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the Department of Health Publications Order Line
0870 1555 455. ref: N0546. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on March 9, 2006. This summary was updated by ECRI on April 16, 2007 following the U.S. Food and Drug Administration advisory on Sedative-hypnotic drug products.

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Date Modified: 9/29/2008

